Applicants respectfully remind the PTO that the firm of Finnegan, Henderson, Farabow, Garrett, & Dunner, L.L.P. is now handling this application as per the Power of Attorney filed on October 31, 1996. The new Attorney Docket No. is 02356.0074-00000.

Applicants submit an Information Disclosure Statement concurrently herewith.

The title has been amended to correct a typographical error.

Support for this amendment can be found throughout the specification, for example, at page 31, line 3 through page 32, line 9, and original claims 1-38. Accordingly, this amendment adds no new matter and entry of this amendment is respectfully requested.

Applicants acknowledge that the present application contains claims to non-elected subject matter. Applicants will cancel those claims from this application upon an indication that the elected claims are allowable.

The specification is objected to and claims 37 and 38 are rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly lacks an enabling disclosure.

The Examiner maintains that the specification does not teach how to obtain the antibodies of claim 37 and the compositions of claim 38. It is alleged that it is unclear whether changes or modifications that occur in the gene will affect the antigenic determinants in order to obtain a composition to treat infection caused by *H. pylori*. Moreover, the Office states that the antigenic determinants or epitopes have not been disclosed for the *H. pylori* urease, which can be used to obtain the antibodies and composition of the claimed invention. How to obtain the fragments of the polypeptides is further unclear according to the Examiner. Therefore, in view of the foregoing, the Office concludes that one skilled in the art would be required to practice undue

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experimentation in order to make and/or use the claimed invention. Applicants respectfully traverse the rejection.

The Federal Circuit has stated the test for the enablement requirement of 35 U.S.C. § 112, first paragraph:

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed.Cir. 1986), cert. denied, 480 U.S. 987 (1987).

Applicants respectfully submit that the specification provides adequate guidance to teach one having skill in the art how to make and use the claimed invention.

Applicants have canceled claims 18, 19, and 37-39. Newly added claims 40-45 recite a purified polypeptide having the amino acid sequence of at least one of the polypeptides selected from the group consisting of UreE, UreF, UreG, UreH, and UreI as shown in Figure 4 (SEQ. ID NOS: 4-7 and 3, respectively), or a fragment thereof. Newly added claims 46-51 recite a purified polypeptide having an amino acid sequence expressed by a gene selected from the group consisting of ureE, ureF, ureG, ureH, and ureI (SEQ ID NO:1) of H. pylori, or a mutant thereof. Although each of these genes is contained within SEQ ID NO:1, each is a distinct gene. In addition, the newly added claims 53-55 are directed to antibodies, that bind to the purified polypeptides of the claimed invention. The compositions of claims 54-56 comprise the antibodies of claim 53-55 and a pharmaceutically acceptable carrier. The compositions of claims 57-59 comprise a polypeptide of the claimed invention and a pharmaceutically acceptable carrier.

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It is believed that these amendments obviate the rejections under 35 U.S.C. § 112, first paragraph.

Applicants respectfully point out that the "fragments" of the purified polypeptides of claim 40 are enabled by the specification. For example, at page 14, lines 27 through page 4, line 9 specifically address the fragments of the claimed invention. In addition, at page 15, lines 1-5, applicants provide a simple assay to determine whether a polypeptide fragment is within the scope of the invention:

> This functional homology can be detected by implementing the following test: 10^9 bacteria are resuspended in 1 ml of urea-indole medium and incubater at 37°C. The hydrolysis of the urea leads to the release of ammonia which, by raising the pH, leads to a colour change from orange to fuchsia.

(Specification at page 15, lines 1-5). Therefore, applicants respectfully submit that it would require only routine experimentation by one having ordinary skill in the art to determine what fragments are useful in the claimed invention.

In addition, applicants direct the Office's attention to the specification, which enables making and using the polypeptides expressed by mutants as set forth in claims 46-51. For example, at pages 35-39 of the specification, applicants teach that cloned DNA of H. pylori was subjected to mutagenesis, wherein insertional mutations and deletions were observed. Out of 24 insertions selected for analysis, 10 derived plasmids lost the ability to hydrolyze urea. (Specification, page 35, last paragraph.) Based on these results, Applicants were able to assess the necessity of the accessory genes in the expression of a functional urease.

Moreover, the assays for identifying, localizing, and analyzing the mutants of the claimed invention are set forth at pages 35-36 of the specification. Applicants teach transforming host

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cells with the resulting mutants of the cloned DNA in plasmids. The transformed host cells were evaluated under nitrogen-limiting conditions to determine the effects of the mutagenesis and digestion of cloned DNA on urease activity. (Specification, page 36, first full paragraph.) Table 2 provides the results of this study. Accordingly, one having skill in the art would readily appreciate how to make and use the claimed invention.

Regarding the method of obtaining the antibodies of the claimed invention, applicants respectfully submit that the specification provides ample support to teach one of skill in the art to make and use the antibodies of the claimed invention. For example, at page 18, last paragraph, applicants teach that:

> The polypeptides of the invention and in particular the polypeptides whose sequence is given above can be used for the production of monoclonal or polyclonal antibodies, or for the detection of antibodies in a biological sample infected by H. pylori.

Moreover, at page 19, the specification describes the methods of obtaining the antibodies of the claimed invention:

> Monoclonal antibodies can be prepared by the hybridoma procedure or by known procedures for the preparation of human antibodies.
> These antibodies can also be prepared according to the procedure described by Marks et al. (J. Mol. Biol. 1991 222, 581-597).

Applicants submit herewith Exhibits 1-3, which describe known methods of making polyclonal and monoclonal antibodies at the time the claimed invention was made.

Thurlow and McKenzie, "Monoclonal Antibodies in Clinical Medicine - A Review", Australian and New Zealand Journal of Medicine, 13(1):91-100 (Feb. 1983) (Exhibit 1), for example, provide an overview of how to make monoclonal antibodies in 1983, well before the

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effective filing date of the instant application. At pages 91-92, the authors provide the steps of immunizing, fusing, screening, and cloning in order to produce monoclonal antibodies. In addition, at page 93 of Thurlow and McKenzie, the authors describe the clinical interests and advantages of monoclonal antibodies. Therefore, one having skill in the art would appreciate how to both make and use the claimed monoclonal antibodies.

In addition, Berzofsky et al., "Antigen-Antibody Interactions and Monoclonal Antibodies", Fundamental Immunology, Second Edition, Raven Press Ltd.: New York (1989), pp. 315-351 (Exhibit 2) further describe antibodies, their production, and activity. At page 316, Berzofsky et al. teach that ". . . antibodies can be raised, by design of the investigator, with specificity for almost any substance known. In each case, one can find antibodies with affinities as high as and specificities as great as those of enzymes for their substrates and receptors for their hormones." (Emphasis supplied.) At pages 347-350, the authors also describe the production of monoclonal antibodies. Thus, raising antibodies against any antigen was well-known in the art before applicants' filing date, and the Berzofsky et al. publication further supports a finding that one having skill in the art would have been able to produce the antibodies of the claimed invention.

Finally, Hurn and Chantler, Methods in Enz., 70: 104-142 (1980)(Exhibit 3) discuss methods for producing and purifying polyclonal and monoclonal antibodies, the preparation of columns where immunological complexes are formed, and the labeling of purified antibodies to ultimately detect immunological complexes.

In view of these three exhibits, it is clear that methods for obtaining the antibodies of the

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claimed invention were known in the art at the time the claimed invention was made. An applicant need not teach and preferably omits descriptions of well known techniques from a patent specification. Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1534, 3 U.S.P.Q.2d 1737, 1743 (Fed. Cir. 1987). The present specification conforms to that preference.

The PTO has the burden of establishing a *prima facie* case of lack of enablement. In re Marzocchi, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). Furthermore, applicants' specification disclosing how to make and use the claimed invention must be taken as in compliance with § 112, first paragraph, unless there is a reason to doubt the objective truth of the disclosure. In re Brana, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1437, 1442 (Fed. Cir. 1995). No reasons sufficient to cast doubt on Applicants' teachings have been provided. One having skill in the art would be capable of practicing the claimed invention, and withdrawal of the enablement rejection is respectfully requested.

Claims 18, 19, 37, and 38 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention.

Applicants have canceled claims 18, 19, 37, and 38 and replaced them with claims 40-59. Applicants believe that the newly added claims render the instant rejection moot. Accordingly, withdrawal of the rejection is respectfully requested.

Claims 18, 19, and 39 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by, or in the alternative, under 35 U.S.C. § 103 as allegedly obvious over Mulrooney et al., Bradley et al., or Tabaqchali et al.

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The Examiner alleges that: Mulrooney et al. teach polypeptides, UreE, UreF, and UreG, and accessory genes for urease activity; Bradley et al. teach *ure* genes for UreE and UreF; and Tabaqchali et al. disclose a nucleotide sequence, which comprise a part of the nucleic acid sequence (2622-2693) corresponding to the gene ureI. Applicants respectfully traverse the rejection.

In Mulrooney et al., the authors describe a urease from Klebsiella aerogenes, wherein the open reading frames (ORFs) ureA, ureB, ureC, ureE, ureF, and ureG were chacterized. The nucleotide sequences corresponding to these genes of K. aerogenes are depicted in Figure 2 of the reference. For example, the ureE gene is said to be depicted at base pairs 2602-3078 of the Mulrooney et al. reference. A comparison between the claimed polypeptide UreE and the Mulrooney et al. UreE polypeptide follows:

MLYLTQRLEIPAA. . . (Mulrooney et al. UreE polypeptide)

MIIERLIGNLRDLN. . .(UreE of the claimed invention).

Furthermore, K. aerogenes is a different species and, indeed, a member of a different genus than H. pylori. Based on the foregoing, it is clear that the polypeptides of the claimed invention differ from those set forth in Mulrooney et al. Accordingly, the Mulrooney et al. reference does not anticipate the claims.

In addition, applicants submit that no motivation is provided to modify the polypeptide of Mulrooney et al. to arrive at the claimed invention. Accordingly, the claims are nonobvious over Mulrooney et al. Withdrawal of the rejections over Mulrooney et al. is respectfully requested.

The "Bradley et al." reference, hereinafter referred to as "Jones and Mobley", describes

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the urease enzyme from Proteus mirabilis. Applicants respectfully submit that the Jones and Mobley reference does not teach the polypeptides, antibodies, and compositions as claimed herein. For example, in Figure 2 of the reference, the nucleotide and amino acid sequences of the P. mirabilis urease genes are provided. It is noted that UreE of Jones and Mobley corresponds to base pairs 3655-4137 in Figure 2. Applicants provide a comparison of the UreE polypeptides of Jones and Mobley and the claimed invention:

Met Lys Lys Phe Thr Gln Ile Ile Asp Gln. . . (Jones and Mobley)

Met Ile Ile Glu Arg Leu Ile Gly Asn Leu . . .(Ure E of the claimed invention).

Furthermore, P. mirabilis is a different species and, indeed, a member of a different genus than H. pylori. As one can clearly ascertain from this comparison, it is clear that these polypeptides are different. In addition, applicants submit that there is no motivation to modify the polypeptides of Jones and Mobley to arrive at the claimed polypeptides. Accordingly, withdrawal of the rejection over Jones and Mobley is respectfully requested.

Applicants submit that the Tabaqchali et al. reference (WO 91/09049) is cited to allegedly teach a nucleotide sequences, which comprises a part of the nucleic acid sequence (2622-2693) and allegedly corresponds to the gene ureI of the claimed invention. The sequence of nucleotides 2622-2693 have 71 nucleotides. However, the ureI gene of the claimed invention corresponds to nucleotide 211 to 795 of the sequence set forth at pages 4-5 of the instant specification. The claimed ureI gene therefore has 584 nucleotides. It is unclear how a nucleotide sequence of only 71 nucleotides can be said to "correspond" to a gene comprised of 584 nucleotides. Indeed, there is no support whatsoever to teach or suggest the isolation of this particular 71 nucleotide base

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fragment from the 2,704 nucleotide sequence described in Tabaqchali et al. In fact, the Tabaqchali et al. reference is directed to oligonucleotides, which are useful as probes and primers. However, the region of nucleotides 2622-2693 is never even suggested as useful as a probe or primer. Thus, there is no teaching or suggestion to even select this particular region of the Tabaqchali et al.

Moreover, applicants respectfully submit that this application is directed to polypeptides. While nucleotides 2622-2693 of the Tabaqchali et al. reference may teach a portion of the ureI gene of the claimed invention, applicants are not claiming nucleic acids in this application. In fact, it is respectfully submitted that the sequence set forth in Tabaqchali et al. does not even teach the amino acids, which correspond to nucleotides 2622-2693. (See Tabaqchali et al. at page 18). Moreover, there is nothing in the reference to teach or suggest the expression of this particular region to obtain a polypeptide of the claimed invention. Accordingly, applicants respectfully submit that this anticipation rejection is improper since the claims are directed to polypeptides, which are neither taught nor suggested by the Tabaqchali et al. reference. Accordingly, withdrawal of the rejection is respectfully requested.

In view of the foregoing, applicants respectfully submit that this application is now in condition for allowance. Applicants request that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, since the proposed amendment does not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner. Moreover, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims is earnestly solicited.

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The Examiner is invited to call the undersigned to discuss any outstanding issues in order to expedite prosecution.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested, and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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By: _____
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Dated: January 21, 1997

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